REMARKS

A Request for Continued Examination, a Copending Letter, an Information Disclosure Statement, and a Request for three-month Suspension of Action were filed on July 26, 2007. However, despite the suspension of action, a Final Office Action issued on September 28, 2007. Based on an Interview of October 18, 2007, between Applicants' representative and Examiner Haghighatian, the Examiner agreed to vacate the September 28 Office Action, and confirmed that the suspension of action was still in effect.

The mentioned three-month suspension of action ends on October 26, 2007. Thus, this Supplemental Amendment is being timely filed.

The Final Office Action of February 26, 2007, is still outstanding, and this supplemental amendment addresses the rejections set forth in that Office Action. Thus, Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims. Applicants note that a new set of claims is being submitted before the Examiner as well as new evidence being submitted herein.

Status of the Claims

In the present Supplemental Amendment, claims 22 and 41 have been amended and claims 64-68 have been added. Also, claims 3-5, 10-12, 17-19, 23, 24, 26, 27, 31, 32, 38, 39, 54 and 60 were previously canceled, and many of the remaining claims are herein canceled herein, without prejudice or disclaimer of the subject matter contained therein. Thus, claims 22, 41, 62 and 64-68 are pending in this application.

No new matter has been added by way of these amendments and new claims. The amendments to claims 22 and 41 have support in the canceled subject matter, such as in claim 44 (referring to the granules and fine granules), page 5, lines 1-2, and page 6, line 3 of the present specification (homogeneous mixtures). Regarding new claims 64, 65, and 67, these claims have support at least in canceled claims 33 and 35. For new claims 66 and 68, please refer the specification at the bottom of page 6. Thus, no new matter has been added.

Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections (as stated in the Final Office Action of February 26, 2007) and allow the currently pending claims.

Issues under 35 U.S.C. § 103(a)

Claims 1, 2, 6-9, 13-16, 20-22, 25, 28-30, 35-37, 40-53, 55-59 and 61-63 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tai (U.S. Patent No. 5,013,557; hereinafter referred to "Tai '557") in view of Kawakami *et al.* (*J. Bioorganic & Med. Chem. Lett.*, Vol. 4, pp. 1429-1446 (1996); "Kawakami") (see pages 2-3 of the Office Action dated February 26, 2007).

Also, claims 33-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tai '557 in view of Kawakami as applied above, and further in view of Morikazu *et al.*

(JP 4-346937; hereinafter "JP '937") (see pages 3-4 of the Office Action of the Office Action February 26, 2007).

Further, claims 1, 2, 6-9, 13-16, 20-22, 25, 28-30, 35-37, 40-53, 55-59 and 61-63 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Diehl (U.S. Patent No. 5,612,026; hereinafter "Diehl '026") in view of JP '937 (see pages 4-5 of the Office Action dated February 26, 2007).

Applicants respectfully traverse, and reconsideration and withdrawal of these rejections are respectfully requested. Applicants note that the rejections of many of the claims are rendered moot since they have been canceled. For instance, regarding the rejection of claims 33-34 in view of Tai '557, Kawakami and JP '937, these claims have been canceled. The remarks below are with respect to the pending claims.

The Bitter Taste of Donepezil Hydrochloride

In the previously filed Amendment dated December 1, 2006, Applicants argued that the unpleasant, basic taste of donepezil hydrochloride was not known at the time the present application was filed. In response, as shown at page 6 of the February 26th Office Action, the Examiner states the rejections are being maintained for several reasons. Applicants respectfully traverse this rejection.

First, regarding the Examiner's comments in the Office Action at page 6, starting at line 12, Applicants maintain that the unpleasant taste of donepezil hydrochloride was not known when the present application was filed. One of ordinary skill in the art was not aware of the

bitter or unpleasant taste of donepezil hydrochloride before the priority dates of the present application. ARICEPT, a trade name of donepezil hydrochloride, was admitted in November, 1996, by the FDA in the form of a film tablet. This dosage form is a tablet that is coated with film, and for this reason there is no unpleasant, bitter taste to the patient ingesting the film tablet. It was not until later that it was discovered that donezepil hydrochloride even had the bitter taste.

To further support Applicants' position, herein enclosed is "**Evidence A**" from the *Instruction Manual for Japanese Pharamcopeia* (13th Ed. 1996), together with an English language translation thereof (3 pages total). Evidence A shows that a coated tablet includes a film-coated tablet and a sugar-coated tablet. The coating itself serves to mask bitterness, an odor or stimulating taste for administration, improvement in light resistance and providing a glossy appearance. In other words, the coating serves multiple purposes. Also, despite the Examiner's comments regarding coatings, the knowledge of only a film-coated tablet does not equate to the knowledge that donepezil hydrochloride has an unpleasant taste.

Applicants also herein attach "**Evidence B**," which is an excerpt from *Modern Pharmaceutics* (Third Ed. 1996). As seen from the includes pages 374-375, a "coated tablet" means coating of tablets, including film-coating, that is carried out for the purpose of masking an unpleasant taste, masking an unsightly appearance of uncoated tablets, increasing patient acceptability, and preventing degradation caused by moisture, air or light. Again, the knowledge of only tablet having a film coating does not equate to the knowledge that donepezil hydrochloride has an unpleasant taste. Coating serves several purposes (e.g., targeted or controlled release), and does not indicate that any specific medicine has an unpleasant taste.

In fact, Applicants respectfully submit that the bitter taste of donepezil hydrochloride was first revealed by Eisai Co., Ltd. in the herein attached literature ("**Evidence C**"), which is an excerpt from the *Technical Report of IEICE OME 2000-80*, titled "Quantification of Taste of Medicines with a Taste Sensor" (pages 125-130, include English language Abstract on page 125). Applicants also note Evidence A, Table 2 (MDHCL, basic hydrochloride), a tested model medicament. It is shown in Figures 2, 3, 4 and 7 and Table 4 that the tested medicament (not until later called donepezil hydrochloride) has an unpleasant taste.

"**Evidence D**" is also herein attached. Evidence D is an excerpt from *Pharm. Tech. Japan*, Vol. 17(9), pp. 31-33 (2001) showing the first public exposure to the name of donepezil hydrochloride. Evidence D shows a method of determining a taste of a medicament quantitatively at page 34, Figure 4 and page 35, Figure 5 that donepezil hydrochloride has a very unpleasant taste.

Thus, Applicants have provided Evidence labeled as A-D showing that one of ordinary skill in the art was not aware of the bitter or unpleasant taste of donepezil hydrochloride before the priority dates of the present application. ARICEPT, a trade name of donepezil hydrochloride, was admitted in November, 1996, by the FDA in the form of a film tablet. This dosage form is a tablet that is coated with film, and for this reason there is no unpleasant, bitter taste to the patient ingesting the film tablet. It was not until later that it was discovered, by Applicants, that donezepil hydrochloride even had a bitter taste. Accordingly, Applicants traverse the Examiner's comments including those shown at page 6 of the Office Action, and request reconsideration in view of this newly submitted evidence.

Official Notice

Further, due to the Examiner's treatment of Applicants' arguments, certain U.S. case law is now relevant. More specifically, the Examiner's comments in the outstanding Office Action are not supported by evidence and thus amount to "official notice" (see especially the comments in the Office Action at page 6, lines 9-12). Thus, Applicants take strong issue with the Examiner's reliance upon "official notice" as a basis for rejecting elements of the claims. The Examiner has made no attempt to provide references, which would presumably exist if such elements were "common knowledge." Applicants direct the Examiner's attention to MPEP § 2144.03(A) which states: "While 'Official Notice' may be relied on, these circumstances should be rare when an application is *under final rejection.*" The present application is under final rejection. Moreover, even if the Examiner has properly taken "official notice", there must be some form of evidence on the record to support such an assertion of common knowledge. In this regard the Examiner is respectfully requested to refer to *In re Zurko*, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001) (holding that general conclusions concerning what is "basic knowledge" or "common sense" to one of ordinary skill in the art without specifying factual findings and some concrete evidence in the record to support these findings will not support an obviousness rejection).

Also, now that Applicants have challenged the Examiner's assertion of official notice, the Examiner must now provide documentary evidence if the rejection is to be maintained. In this regard, the Examiner is requested to refer to 37 C.F.R. §1.104(c)(2) and *Zurko*, 59 USPQ2d at 1697.

> Alternatively, if the Examiner is relying upon personal knowledge to support the finding of what is known in the art, the Examiner is respectfully requested to provide an affidavit or declaration setting forth specific factual statements and explanations to support such a finding. In this regard the Examiner is referred to 37 C.F.R. §1.104(d)(2).

In addition, Applicants respectfully submit that the discovery of the problem itself can be a basis for patentability. Specifically, the Federal Circuit has held that the invention as a whole is not restricted to the specific subject matter claimed, but also embraces its properties and the problem(s) it solves. *In re Wright*, 6 USPQ2d 1959, 1962 (Fed. Cir. 1988) ("The problem solved by the invention is always relevant. The entirety of a claimed invention, including the combination viewed as a whole, the elements thereof, and the properties and purpose of the invention, must be considered"); *In re Sponnoble*, 160 USPQ 237 (CCPA 1969). In other words, discovery of a problem is inventive even if once discovered, the solution is obvious. Applicants further note: "It should not be necessary for this court to point out that a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. 103." *In re Antonson*, 47 CCPA 740, 272 F.2d 948, 124 USPQ 132 (CCPA 1959). Here, Applicants were first to discover the problem of the bitter taste of donepezil hydrochloride and this should be taken into consideration, especially from the perspective at the time the present application was filed.

Other Reasons as to Why These Rejections Have Been Overcome

Applicants also maintain the previous arguments of record (see the response dated December 1, 2006). For instance, the cited Kawakami *et al.* reference gives no description of the unpleasant taste of E2020 to the patient and thus the Examiner is using Kawakami *et al.* only for disclosing donepezil hydrochloride and is improperly combining Kawakami *et al.* with the other references.

As another instance, the cited Tai '557 reference shows a spraying-dried product including sucralfate and that the unpleasant taste-masking action is caused by a matrix imposed on microcapsules (B), which is not the present invention as claimed. In the present invention, upon oral administration, the electric interaction is produced which masks the bitter taste of the basic medicine. The cited Tai '557 reference fails to show the combination of the instantly claimed invention, as well as the claimed electric interaction and homogeneous blend.

Furthermore, the reference in the Office Action to sucralfate as being a basic medicine is improper. Sucralfate is also generically known as "basic aluminum sucrose sulfate" and is an aluminum salt of an acidic medicine (sucrose sulfate). However, because of the aluminum salt, sucralfate is actually a basic medicine. This is contrast to donepezil hydrochloride which is a hydrochloride of a basic medicine (donepezil). Donepezil hydrochloride is an acidic medicine. Though the present specification refers to donepezil hydrochloride as a basic medicine, the reason for this description is that donepezil hydrochloride means a hydrochloride of a basic medicine (donepezil) (in contrast to sucralfate which is an aluminum salt of an acidic medicine

of sucrose sulfate). In other words, sucralfate and donepezil hydrochloride are medicines having completely opposite charges and different properties from each other.

Regarding the Tai '557 disclosure of sucralfate, the effect of masking an unpleasant taste by adding donepezil hydrochloride and an acidic polysaccharide according to the claimed invention is due to the formation of an ionic complex by the positive-charged donepezil hydrochloride (a basic medicine) and the negative-charged acidic polysaccharide. But in contrast to the present invention, and as described above, sucralfate is a basic aluminum sucrose sulfate having a negative charge, and therefore does not form a complex by an ionic interaction as is formed in the claimed invention. In fact, the mechanism for masking a bitter taste of sucralfate is different. The aluminum component (of a salt of sucralfate) and alginic acid are blended together, wherein moisture from water or from the oral cavity is taken in. The bitter substance (sucralfate) is present in the gel state, and the area of contact with the specific region of the tongue (which tastes the bitterness) is reduced. As a result, the bitterness can be prevented or reduced, but this mechanism is completely different from the masking effects of the presently claimed invention. Accordingly, Applicants respectfully maintain that the cited combination of references do not describe the present invention's advantage of masking the bitter taste of donepezil hydrochloride.

Regarding the cited Diehl '026 reference, this reference discloses a drink mix composition containing 1) an anion exchange resin, 2) Xanthan (gelation agent) and 3) an edible water-soluble salt (maltodextrin). However, there is also the following description in lines 40 to 55 of Column 5 of Diehl '026:

> The present compositions may optionally contain one or more sweetening agents. The sweetening agents include saccharides, polysaccharides such as xylose, ribose, glucose....

That is, a polysaccharide is added as a sweetening agent in the cited Diehl '026 reference, and examples of saccharides exemplifies after "such as" all have a sweet taste. This is in contrast to the instantly claimed invention which contains an acidic polysaccharide having no sweet taste, i.e., is not a sweetening agent. Further, carrageenan, chondroitin sulfate and dextran sulfate (also instantly claimed) are not disclosed in the cited Diehl '026 reference.

The further combination with Morikazu '937 is also improper. In the cited Morikazu '937 reference, the disclosed technique is limited to a jelly medicine. The claimed invention, however, is not a jelly medicine, a syrup or a liquid medicine. Further, the agar, gelatin and K-carrageenan added to a jelly medicine, described in Morikazu '937 are gelation agents for solidifying (gelatinizing) in a mold as a jelly medicine, and are generally used for jelly medicines. In contrast, the carrageenan used in the granule medicine, fine granule medicine, powder medicine or tablet (according to the claimed invention) does not reduce the bitterness by the effect of the gelation agent, but by the mechanism of action for forming a complex by an ionic interaction between donepezil hydrochloride and the acid polysaccharide. Accordingly, the cited Morikazu '937 reference is completely different from the claimed invention.

Moreover, Morikazu '937 does not disclose or teach the ionic interaction as claimed. Morikazu '937 discloses a method of reducing a bitterness by adding 1) a substance having a bitterness, 2) a gelation agent selected from agar, gelatin and K-carrageenan, and 3) a flavoring agent to give a flavored jelly form. However, in Example 1 of Morikazu et al., tannic acid being

an acidic substance. Also, in Example 2, Morikazu '937 discloses a mixture of acidic compounds as the principal components, and in its Example 3, soy peptide are used as the 1) substance having a bitterness, respectively. That is, a basic medicine used in the claimed invention is not used.

Therefore, the Morikazu '937 substance having a bitterness will never have a positive charge and/or form an ionic complex. Instead, Morikazu '937 uses other masking ingredients and not the mechanism of action of forming a complex by an ionic interaction as instantly claimed.

Thus, the requisite motivation and/or reasonable expectation of success are lacking with respect to the all outstanding rejections as the references are improperly combined.

Summary

Thus, this outstanding § 103(a) rejections have been overcome for any and all reasons stated above. Reconsideration and withdrawal of these rejections are respectfully requested.

Conclusion

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez, Reg. No. 48,501,

at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

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Attachments:

- **Evidence A**: Excerpt from the *Instruction Manual for Japanese Pharamcopeia* (13th Ed. 1996) with English language translation thereof (total of 3 pages)
- **Evidence B**: Excerpt from *Modern Pharmaceutics* (Thirteenth Ed. 1996) (4 pages total
- **Evidence C**: Excerpt from *Technical Report of IEICE OME 2000-80*, "Quantification of Taste of Medicines with a Taste Sensor" (pages 125-130, include English language Abstract on page 125)
- **Evidence D**: Excerpt from *Pharm Tech Japan*, Vol. 17(9), pp. 31-33 (2001)